IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

MALLINCKRODT INC.,	*	
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Plaintiff,	*	
	*	
v.	*	Civil No. 14-CV-3607-DKC
	*	
UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.,	*	
	*	
	*	
Defendants.	*	
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DEFENDANT'S MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR TEMPORARY RESTRAINING ORDER

Plaintiff Mallinckrodt, Inc. ("Mallinckrodt") filed this case seeking the extraordinary relief of requiring the United States Food and Drug Administration ("FDA") to change the "therapeutic equivalence" or TE rating for Mallinckrodt's generic drug product, methylphenidate hydrochloride extended release tablets, which is used to treat children and adults with Attention Deficit Hyperactivity Disorder ("ADHD"). Plaintiff makes this bold request despite serious unresolved scientific questions posed by FDA about whether Mallinckrodt's product in fact provides the same continuous therapeutic effect as the brand-name product. *See* Ex. A, FDA Oct. 30, 2014, Memo. More fundamentally, all of Mallinckrodt's claims, are premised on the assumption that FDA's change in the TE rating for its product is tantamount to withdrawing approval of the product. In fact, Mallinckrodt's product is still approved and can continue to be marketed. FDA's well-established practice of publishing advisory TE ratings in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") (34th ed. 2014) is vastly different from the statutory drug approval and withdrawal process contained in 21 U.S.C. § 355(e), despite Mallinckrodt's characterizations to the contrary.

Plaintiff's motion is wholly without merit and falls well short of meeting the heavy burden required for issuance of a temporary restraining order. Not only is Plaintiff unlikely to succeed on the merits because it cannot establish any of its asserted claims under the Administrative Procedure Act ("APA") or the Constitution, but judicial review of a change in TE ratings is precluded under the APA because it does not constitute final agency action. None of the other preliminary injunction factors support Mallinckrodt's request. Mallinckrodt's desire to protect its business revenue does not come close to meeting the threshold of irreparable harm required to obtain the extraordinary relief requested, and the public interest is simply not advanced by forcing FDA to change the TE rating for Mallinckrodt's product in the face of unresolved scientific questions.

For the reasons set forth herein, the Court should deny Mallinckrodt's motion for a temporary restraining order.

BACKGROUND

I. Statutory and Regulatory Background

Under the Food, Drug, and Cosmetic Act ("FDCA"), there are multiple pathways for approval of a new drug product, including the New Drug Application ("NDA") process, *see* 21 U.S.C. § 355(b)(1) & (b)(2), and the Abbreviated New Drug Application ("ANDA") process, *see* 21 U.S.C. § 355(j) – the pathway for the Mallinckrodt product. There are important differences in the approval requirements for each pathway. Pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing an NDA containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b).

The FDCA permits an applicant to submit an ANDA seeking approval for a generic version of a previously approved drug product (a "duplicate"). 21 U.S.C. § 355(j). This previously approved drug is called the reference listed drug ("RLD"), defined as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. § 3l4.3(b). ANDA applicants rely on FDA's finding of safety and effectiveness for the RLD and do not submit the same types of clinical investigations to demonstrate safety and effectiveness, as are necessary for approval of an NDA. Rather, an application for a generic version of the RLD must demonstrate that it is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and with certain exceptions, labeling. *See e.g.*, 21 U.S.C. §§ 355(j)(2)(A) & 355(j)(4); *see also* 21 C.F.R. § 314.94. An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD. *See, e.g.*, 21 U.S.C. §§ 355(j)(2)(A)(iv) & 355(j)(4)(F). A drug is considered to be bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . . ." 21 U.S.C. § 355(j)(8)(B)(i). FDA will approve the ANDA unless it finds that there is insufficient evidence of the foregoing or there is inadequate information to ensure the identity, strength, quality, and purity of the drug. *See e.g.*, 21 U.S.C. §§ 355(j)(2)(A) & 355(j)(4); *see also* 21 C.F.R. § 314.94.

FDA considers drug products to be TE "only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." *See* Orange Book Preface at vii. Drug products are considered pharmaceutical equivalents if they contain the same active ingredients, are

of the same dosage form and route of administration, and are identical in strength or concentration. *See* 21 C.F.R. § 320.1(c); Orange Book Preface at vi-vii. Thus, products evaluated as TE can be expected, in the judgment of FDA, to have equivalent clinical effect. Orange Book Preface at xi. The Orange Book also sets forth general criteria for evaluating TE, including, among others, pharmaceutical equivalence and bioequivalence. *Id.*

FDA first published the above-described TE rating criteria in 1980, in the context of a notice-and-comment rulemaking amending FDA's disclosure regulations. *See* 45 Fed. Reg. 72582 (Oct. 31, 1980); *see also* 44 Fed. Reg. 2932 (Jan. 12, 1979) (proposed rule); codified in FDA's disclosure regulations at 21 C.F.R. § 20.117. This notice-and-comment rulemaking put sponsors and the public on notice that FDA will make TE ratings publicly available using the above criteria. Each subsequent edition of the Orange Book includes new approvals and updated TE ratings, as appropriate. *See* Orange Book Preface at v. The current thirty-fourth edition of the Orange Book is available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

A product's TE rating is designated by the particular TE code assigned to it. The first letter of a TE code reveals whether or not FDA has evaluated a product as TE to another product, while the second letter provides additional information regarding the bases of FDA's evaluation. *See* Orange Book Preface at xiii. TE codes fall into two basic categories: (1) those that begin with the letter "A" (signifying that FDA considers the product to be TE to another product); and (2) those that begin with the letter "B" (signifying that, at the time of the rating, actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. *See id.*

The Orange Book is informational and advisory. Orange Book Preface at xi. It is a mechanism for the public to gain access to existing agency information or records. *See* Orange Book Preface at xi ("To the extent that the [Orange Book] identifies drug products approved under [21 U.S.C. § 355], it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act."). The Orange Book's TE ratings do not constitute determinations that any product violates the Act or its implementing regulations. *Id.* Nor does the Orange Book mandate which drug products may or may not be purchased, prescribed, dispensed, or substituted for one another. *Id.*

Consistent with its goal to provide the public with the agency's most current TE information, FDA may change a product's TE rating if the circumstances giving rise to the rating change or information available to the agency calls into question the data FDA assessed to evaluate a product's TE rating. Orange Book Preface at xiii. When TE rating changes apply to a single drug product, as opposed to an entire category of drug products, FDA does not initiate notice and comment rulemaking.[1] *Id.* at xiii, xii.

II. Factual Background

On December 28, 2012, Mallinckrodt obtained FDA approval of a generic version of the RLD drug Concerta,[2] methylphenidate hydrochloride extended release ("ER") tablets, under ANDA

[1] Mallinckrodt's product is a generic of Concerta, which is only one of the approved methylphenidate hydrochloride products. *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=METHYLPHENIDATE%20HYDROCHLORIDE. FDA did not make any changes to the TE ratings for products referencing methylphenidate products other than Concerta.

[2] Concerta is manufactured by Janssen Pharmaceuticals, Inc. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/21121ltr.pdf. Approved generic

202608. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202608Orig1s000ltr.pdf. The product was approved for the treatment of ADHD in children and adults 6 years of age and older. *Id.* At the time of approval, the TE rating for Mallinckrodt's product in the Orange Book was designated AB, meaning that FDA considered Mallinckrodt's generic methylphenidate hydrochloride ER product to be TE to Concerta.

Mallinckrodt's methylphenidate hydrochloride product, like Concerta, is intended to control ADHD symptoms by releasing the drug in the body over a 10- to 12-hour timeframe of daily living (e.g., school or work) and not to interfere with the ability of the patient to sleep at night. *See* Ex. A at 1. In some individuals, however, evidence suggests that Mallinckrodt's products may deliver the drug in the body at a slower rate during the 7- to 12-hour range. *Id.* at 12-13. The diminished release rate may result in the product not having the desired therapeutic effect. *Id.*

Shortly after Mallinckrodt received approval, FDA began to receive adverse event reports and complaints relating to the product's lack of effect. *See* http://www.fda.gov/Drugs/DrugSafety/ucm422569.htm. Between May 2013 and June 2014, FDA's Adverse Event Reporting System ("FAERS") database received reports of patients describing insufficient therapeutic effect, including nearly 200 adverse event reports about the Mallinckrodt product. *Id.*

Although the total number of lack-of-effect reports was small compared to the overall usage of methylphenidate hydrochloride products, FDA evaluated the overall number of complaints for

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versions of Concerta are manufactured by Mallinckrodt and Kudco. *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=METHYLPHENIDATE%20HYDROCHLORIDE. Janssen also manufactures an "authorized generic" of Concerta, which is marketed by Actavis as a generic. *Id.* Because the Actavis drug is identical to Janssen's Concerta and was not subject to the same TE concerns as Mallinckrodt's and Kudco's products. *Id.*

Mallinckrodt generic products relative to the brand-name and authorized generic products and found substantially more complaints for the two generic products. After learning of concerns with the products, the Office of Generic Drugs in FDA's Center for Drug Evaluation and Research ("CDER") conducted a multi-disciplinary review of the products, which included an evaluation of adverse event reports; a review of the data submitted with the ANDAs; FDA laboratory testing, including drug stability and dissolution testing; and broad interdisciplinary consultation with FDA physicians, pharmacists, chemists, and other agency scientists and experts to discuss the new information. *See* Ex. A at 3-14.

As a result of FDA's analysis of adverse event reports, internal re-examination of previously submitted data, and FDA laboratory tests, on November 12, 2014, FDA notified Mallinckrodt that the agency has reason to believe that Mallinckrodt's methylphenidate hydrochloride ER tablets may not be therapeutically equivalent to Concerta. Ex. A at 14. On November 13, 2014, FDA updated the Orange Book accordingly by changing the TE code for Mallinckrodt's product from AB to BX. This means that Mallinckrodt's methylphenidate hydrochloride ER product remains approved and can be prescribed, but the data that have been reviewed by the agency are insufficient to determine TE to Concerta.

As FDA told Mallinckrodt, FDA expects Mallinckrodt to either: (1) voluntarily withdraw its products from the market under 21 C.F.R. § 314.150(d) and request that FDA withdraw approval of the ANDA; or (2) commit to complete new bioequivalence studies on its product within 6 months in accordance with FDA's Revised Draft Guidance on Methylphenidate Hydrochloride (Nov. 2014).

See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf.[3]

ARGUMENT

I. Standard of Review

A temporary restraining order is an "extraordinary and drastic" remedy that "may only be awarded upon a clear showing that the plaintiff is entitled to such relief." *Winter v. NRDC, Inc.*, 555 U.S. 7, 22 (2008); *Munaf v. Geren*, 553 U.S. 674, 689-90 (2008). To obtain a temporary restraining order, a party must establish that: (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) an injunction would serve the public interest. *Winter*, 555 U.S. at 22. Mallinckrodt fails to meet all four elements.

II. Mallinckrodt Has Failed to Demonstrate a Substantial Likelihood of Success on the Merits

Mallinckrodt cannot establish a likelihood of eventual success on the merits for any of its claims. For that reason alone, the Court should deny Mallinckrodt's request for extraordinary, emergency relief. *See Munaf*, 553 U.S. at 689-90.

A. The TE Rating for Mallinckrodt's Product Is Not Final Agency Action and Thus Not Subject to Judicial Review

To be reviewable under the APA, the agency conduct in question must (1) constitute "agency action" and (2) be "final." *Golden & Zimmerman, LLC v. Domenech*, 599 F.3d 426, 431

[3] The original draft guidance recommendations for bioequivalence testing for Mallinckrodt's product (published in September 2012, and in effect at the time of ANDA 202608's approval) were developed using the best information then-available. *See* http://www.fda.gov/Drugs/DrugSafety/ucm422569.htm.

(4th Cir. 2010). The APA defines "agency action" as including "the whole or a part of an agency rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act." 5 U.S.C § 551(13).

The TE rating for Mallinckrodt's drug product does not constitute agency action, as the court in *Pharmaceutical Mfrs. Ass'n v. Kennedy*, 471 F. Supp. 1224 (D.Md. 1979) concluded. In that case, the court dismissed a suit filed by the Pharmaceutical Manufacturers Association ("PMA") challenging FDA's publication of TE ratings. 471 F. Supp. at 1225. The court held that although the TE ratings may adversely affect PMA members, the TE ratings did not "order[] any PMA member to engage in or refrain from any action. Nor is any agency doing anything which is binding on the parties." 471 F. Supp. at 1231 (internal citation omitted). Accordingly, there was no judicially reviewable agency action under the APA. *Id.*

FDA explained in the original Orange Book notice-and-comment rulemaking that TE ratings are advisory, informational, and non-binding. *See e.g.*, Orange Book Preface at xi, xii-xiii; 45 Fed. Reg. 72584-89. TE ratings do not determine the legal rights of any drug manufacturer or distributor, nor impose any requirement or restriction upon any person. *See e.g.*, Orange Book Preface at xi, xii-xiii; 45 Fed. Reg. 72584-89; *see also Pharm. Mfrs. Ass'n*, 471 F. Supp. at 1231 (affirming that TE ratings are advisory).

Even if FDA's change to a product's TE rating could be considered agency action, it would not be "final." To be final, "the action must be one by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 177 (1997) (internal citations omitted). Mallinckrodt can point to no right or obligation that stems

directly from a change in TE rating rather than an intervening act by a third party (i.e., a pharmacist). Indeed, even in the unpublished opinion relied on by Mallinckrodt, *see* TRO Br. at 32, where the court, *in dicta*, theorized that an Orange Book designation might constitute final agency action, the court stated that it need not ultimately resolve that issue, determined that the Orange Book listing with TE rating was not arbitrary and capricious, and did not require FDA to undergo notice-and-comment rulemaking or other additional processes. *Zeneca Inc. v. Shalala*, No. Civ. A. WMN-99-307, 1999 WL 728104 (D.Md. Aug. 11, 1999).

The existence of some state pharmacy statutes incorporating FDA's TE ratings or any purported harm sustained as a result of Mallinckrodt's product's TE rating do not render an agency action final. As the D.C. Circuit has held, materials promulgated by a federal agency and later adopted as part of a local government's permitting process do *not* create a binding effect and are thus not subject to judicial review. *Nat'l Ass'n of Home Builders v. Norton*, 415 F.3d 8, 14-16 (D.C. Cir. 2005); *cf.* TRO Br. at 33 (emphasizing the legal consequences that flow from the Mallinckrodt TE listing under state pharmacy laws). Likewise, "an agency's action is not final agency action merely because it betokens harm." *See, e.g.*, *Sierra Club v. Peterson*, 185 F.3d 349, 377 (5th Cir. 1999) (citation omitted).[4]

[4] It bears mentioning that, even assuming that an FDA employee represented to Mallinckrodt during FDA's November 12, 2014 conference call that the drug product's TE rating constituted final agency action, which FDA disputes, any such unofficial statement of a subordinate FDA official "does not bind or otherwise obligate or commit the agency to the views expressed." 21 C.F.R. § 10.85(k); *see also* TRO Br. at 31. Moreover, courts have consistently held that statements of subordinate agency officials and other similar informal statements do not represent final agency action and are not reviewable. *See, e.g.*, *Holistic Candlers & Consumers Ass'n v. FDA*, 664 F.3d 940 (D.C. Cir.) (warning letters, even in combination with FDA's website posting

B. Even Assuming Arguendo that FDA Took Agency Action, It Was Not Arbitrary and Capricious or Otherwise Unlawful

Mallinckrodt asserts corollary challenges against FDA under the APA, 5 U.S.C. § 706(2)(B), and the Fifth Amendment. Complaint ¶¶ 33-46.[5] The APA gives courts power to review agency action and to hold it unlawful, if found to be 'contrary to constitutional right, power, privilege, or immunity." 5 U.S.C. § 706(2)(B). The Due Process Clause of the Fifth Amendment provides: "No person shall . . . be deprived of life, liberty, or property, without due process of law . . . ." U.S. Const., Am. V. Both claims are predicated on Mallinckrodt having a constitutionally protected property right in its TE rating, which it does not. *Cf. Bd. of Regents of State Colleges v. Roth*, 408 U.S. 564, 569-70 (1972) (Fifth Amendment requires procedural due process only where a person is deprived of a protected interest in liberty or property).

Mallinckrodt argues that the drug approval serves as the source for its purportedly protected property interest and that the agency deprived Mallinckrodt of that property interest when it changed the TE rating. Complt. ¶¶ 34-35. But, in order for that property interest to be deprived, the agency would have had to withdraw the drug's approval under 21 U.S.C. § 355(e). Withdrawal entails, among other things, notice and opportunity for a hearing to the applicant and a formal determination by the Secretary that a drug product meets the criteria set forth in 21 U.S.C. § 355(e),

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and FDA representatives' statements, were insufficient to supply the finality necessary for review of agency action).

[5] Recognizing the absence of agency action under the APA, Mallinckrodt separately challenges methylphenidate hydrochloride ER's TE rating change under the Fifth Amendment's Due Process Clause. TRO Br. at 18 & n.7.

such as a showing by scientific data that the drug is unsafe or ineffective. The agency has taken no such action.

Mallinckrodt does not allege otherwise. Rather, Mallinckrodt argues that, FDA has "effectively" withdrawn its approval, because the drug is not on the marketplace to the same extent it was with the AB rating. *See, e.g.*, TRO Br. at 15. Diminished marketplace availability does not equate to withdrawal of a drug approval. Mallinckrodt's ANDA for its methylphenidate hydrochloride products has been and currently is approved, and Mallinckrodt currently commercially markets these products. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202608Orig1s000ltr.pdf. Mallinckrodt's repeated reliance on "constructive withdrawal" as a "legitimate claim of entitlement" is misplaced.[6]

A change in the TE rating by itself is a far cry from a cognizable property interest. While certain state laws may limit the purchase or substitution of Mallinckrodt's product following the TE rating change, that does not somehow vest Mallinckrodt with a constitutional property interest. The TE rating change in and of itself has not prohibited or limited the product's sale or purchase or altered its legal status under the FDCA.

Nor is Mallinckrodt likely to succeed on the merits of its claim that FDA has exceeded its statutory authority by taking its methylphenidate hydrochloride ER tablets "off the market without satisfying the evidentiary standard of 21 U.S.C. § 355(e)." TRO Br. at 20. As noted above, FDA changed the TE rating for Mallinckrodt's product in the Orange Book from AB to BX, but the product's legal status has not changed: Mallinckrodt's product remains an approved drug product

[6] If Mallinckrodt fails to demonstrate bioequivalence and the agency takes further action, all appropriate procedural protections would apply.

under the FDCA. *See* FDA Statement, Methylphenidate Hydrochloride Extended Release Tablets (generic Concerta) made by Mallinckrodt and Kudco, available at http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm. At this time, FDA has not initiated the process to withdraw approval pursuant to 21 U.S.C. § 355(e). Accordingly, the agency has not acted in excess of statutory authority, or short of a statutory right under the APA, 5 U.S.C. § 706(2)(C), especially for action it has not taken (i.e., withdrawal of a NDA).

C. Notice-and-Comment Rulemaking Was Not Required Before FDA Issued the 2014 Draft Guidance on Methylphenidate Hydrochloride

Mallinckrodt's challenge to the guidance document is meritless. FDA was not required to undergo notice-and-comment rulemaking before issuing the 2014 Draft Guidance on Methylphenidate Hydrochloride.[7] FDA's regulatory interpretation, as described in the draft guidance document, constituted, at most, an interpretive rule. An interpretive rule is not subject to the notice-and-comment procedures for legislative rules set forth in Section 553 of the APA. 5 U.S.C. § 553(b)(A).

"[A]n interpretive statement simply indicates an agency's reading of a statute or rule. It does not intend to create new rights or duties, but only reminds affected parties of existing duties." *Orengo Caraballo v. Reich*, 11 F.3d 186, 195 (D.C. Cir. 1993) (quotation omitted). To be exempt from the notice-and-comment procedures, an interpretive rule need not simply paraphrase statutory or regulatory language. *Id*. Instead, it may "suppl[y] crisper and detailed lines than the authority

[7] Nor did the issuance of the draft guidance have any impact on the change of Mallinckrodt's TE rating, which FDA changed independently of issuing the new draft guidance.

being interpreted." *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993).

The D.C. Circuit examines four factors to determine whether a rule is interpretive (and thus exempt from notice-and-comment procedures) or legislative (and thus subject to notice-and-comment procedures). "If the answer to any of [the following] questions is affirmative, we have a legislative, not an interpretive rule." *Am. Mining Cong.*, 995 F.2d at 1112.

> (1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties,
> (2) whether the agency has published the rule in the Code of Federal Regulations,
> (3) whether the agency has explicitly invoked its general legislative authority, or
> (4) whether the rule effectively amends a prior legislative rule.

Id.

Here, the answer to each of these questions is "no." First, even in the absence of the "rule" in question — FDA's bioequivalence recommendations described in the draft guidance — the agency would have discretion to determine what types of evidence and metrics are sufficient to demonstrate bioequivalence for a given product. That authority stems from the plain language of FDA's bioequivalence regulations set forth at 21 C.F.R. part 320, as well as the statutory and regulatory provisions requiring an ANDA to include information showing bioequivalence, *see* 21 U.S.C. §§ 355(j)(2)(A)(iv) and (j)(4)(F); 21 C.F.R. § 314.94(a).[8] FDA identified these authorities,

[8] For example, FDA's regulations provide (i) the types of evidence to measure the bioavailability or establish bioequivalence, (ii) guidelines for the conduct of an in vivo bioavailability study, (iii) guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study, and (iv) criteria and evidence to assess actual or potential bioequivalence

among others, in guidance establishing the process for issuing product-specific BE recommendations. *See* Guidance for Industry: Bioequivalence Recommendations for Specific Products (June 2010) at 1–2, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072872.pdf. Also in that guidance document, and consistent with the view that the FDA has the authority to act absent the bioequivalence recommendations, the agency noted that "FDA is not required to publish draft or final product-specific BE recommendations before it approves an ANDA for the drug product." *Id.* at 3.

Second, FDA did not publish the challenged interpretation of Section 320.24 (i.e., the draft guidance) in the Code of Federal Regulations. Instead, it appears in a draft guidance. Third, FDA has not explicitly invoked its general legislative authority in support of its interpretation of Section 320.24.

Finally, FDA has not "effectively amend[ed]" a prior legislative rule through its interpretation. As set forth above, FDA's interpretation, embodied in the draft guidance, is consistent with the plain language of Sections 320.20, 320.22, and 320.24. FDA's interpretation of the bioequivalence regulations therefore did not "repudiate," nor "is [it] irreconcilable with" the language of the regulation — essential requirements of the "effective amendment" doctrine. *See Am. Mining Cong.*, 995 F.2d at 1109, 1112; *see also Nat'l Family Planning & Reprod. Health Ass'n v. Sullivan*, 979 F.2d 227, 235 (D.C. Cir. 1992) (the relevant inquiry is whether an agency's

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problems. *See* 21 C.F.R. §§ 320.24–26, 320.33. These regulations, among others, are the bases for the bioequivalence recommendations made in the draft guidance at issue here.

"subsequent interpretation runs 180 degrees counter to the plain meaning of the regulation."). Thus, the answer to all four of the *American Mining Congress* questions is "no."

Moreover, the draft guidance does not have any other hallmarks of a legislative rule, such as a "binding effect" on private parties or on the agency. *Am. Mining Congress*, 995 F.2d at 1112; *Cement Kiln Recycling Coalition v. EPA*, 493 F.3d 207 (D.C. Cir. 2007).[9] The draft guidance, on its face, describes its contents as the agency's current thinking on a topic; does not purport to confer any rights or obligations, bind FDA, or the public; and allows entities to develop alternative approaches to the recommendations:

> This draft guidance, once finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

2014 Draft Guidance on Methylphenidate Hydrochloride. Similarly, the Federal Register notice announcing the availability of the draft guidance for industry states:

> This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on the design of BE studies to support ANDAs for CONCERTA (methylphenidate HCl) extended-release tablets. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

[9] In *Cement Kiln Recycling Coalition v. EPA*, 493 F.3d 207 (D.C. Cir. 2007), the court described the factors for distinguishing legislative rules from policy statements (which, like interpretive rules, are not subject to notice-and-comment rulemaking) as "(1) the Agency's own characterization of the action; (2) whether the action was published in the Federal Register or Code of Regulations; and (3) whether the action has binding effects on private parties or on the agency." *Id.* at 226–27.

79 Fed. Reg. 65,978, 65,979 (Nov. 6, 2014) (emphasis added). The referenced good guidance practices regulations, which are being applied to the 2014 Draft Guidance on Methylphenidate Hydrochloride, likewise state that guidance documents "represent the agency's current thinking," permit "alternative approach[es]" that comply with the relevant statutes and regulations, and neither "establish legally enforceable rights or responsibilities" nor "legally bind the public or FDA." 21 C.F.R. § 10.115(d). For all these reasons, FDA's 2014 Draft Guidance on Methylphenidate Hydrochloride is not a legislative rule and it was not required to engage in notice-and-comment rulemaking prior to its issuance.

D. FDA Properly Found that Mallinckrodt's Products Warrant BX Rating

FDA appropriately changed the TE rating for Mallinckrodt's products from AB to BX. "The code BX is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence." Orange Book Preface at xix. Drugs products assigned the BX rating "are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence." *Id.* The evidence FDA reviewed during its investigation led the agency to conclude that "Mallinckrodt's products may not be therapeutically equivalent to Concerta." Ex. A. at 14. On November 12, 2014, the agency relayed that conclusion to Mallinckrodt and asked the company to commit to completing new bioequivalence studies in accordance with the new guidance within six months. On November 13, the agency changed the TE rating reflecting its conclusions at that time. Until the agency has had the opportunity to consider what, if any, data Mallinckrodt may choose to submit, FDA is not making a final decision regarding therapeutic equivalence for these products.

Given this posture, FDA reasonably determined that the reviewed data was insufficient to determine therapeutic equivalence and assigned the BX rating to Mallinckrodt's products.

FDA's scientific conclusions are entitled to considerable deference. *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) (The FDA is "peculiarly suited" to evaluate conflicting scientific reports, a matter "not . . . well left to a court without chemical or medical background," because it "necessarily implicates complex chemical and pharmacological considerations."). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)).

Mallinckrodt criticizes FDA for not stating in its memorandum that the data "are insufficient to determine therapeutic equivalence." TRO Br. at 23. Mallinckrodt also argues that the agency's decision to change the TE rating was not a product of reasoned decisionmaking. TRO Br. at 23. Nothing could be farther from the truth. In its 15-page memorandum, FDA explained how it evaluated complaints of therapeutic failures, evaluated the product, performed statistical analyses, reviewed bioequivalence data, reviewed clinical pharmacology data, considered clinical observations, and calculated reporting rates and rate ratios. FDA Mem. at 12–13. Unhappy with the TE rating change for its products, Mallinckrodt attempts to poke holes at the data and methodology FDA used, but none of their jabs alters the agency's conclusion regarding therapeutic inequivalence. Mallinckrodt criticizes the agency's reliance on adverse event reports relating to

other products, but it does not dispute that the agency also relied on adverse event reports relating to *Mallincrkrodt's* products. TRO Br. at 24–25. Relying on "[c]ommon sense," Mallincrkodt complains that "FDA considered 'lack-of-effect' complaints that do not relate to therapeutic equivalence, TRO Br. at 25, but again, Mallincrkodt does not dispute that FDA considered "lack-of-effect" complaints that *are* evidence of therapeutic equivalence. Mallincrkodt notes that the agency identified the wrong date by which *one* of its product entered the market, but leaves untouched the relevant part of the agency's comment—that the spike of adverse event reports in April may be attributable to Mallincrkodt's product. TRO Br. at 26. Contrary to Mallinckrodt's assertion, TRO Br. at 26–27, FDA has not "rejected a key assumption" underlying the modeling method it used in evaluating Mallincrkodt's product. The agency's public statement that there is a lack of "authoritative literature information on the correlation of dose or plasma concentration with clinical effects of methylphenidate" does not mean that there is *no* correlation between concentration and clinical effects, so FDA's statement was wholly consistent with its use of a modeling approach that assumes a correlation exists. TRO Br. at 27. Lastly, the fact that the agency did not acknowledge all the data in its possession in a 15-page memorandum does not undermine the agency's conclusion that Mallinckrodt's products may not be therapeutically equivalent to Concerta. *Id.*

In Mallinckrodt's view, the agency's failure to recite the precise words renders the agency's BX assignment arbitrary and capricious. *Id.* But the "magic words" in the BX rating definition need not appear for the court to conclude that the agency made the requisite finding. The APA does not require the agency to formulaically recite the BX definition in order for its BX assignment to be sustained, and the court's decision should not turn, mechanically, on the absence of "magic words."

Courts are required to "uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned." *Bowman Transp. Inc.*, 419 U.S. 281, 286 (1974). FDA's reasoning for assigning the BX code to Mallinckrodt's products is easily discerned from the memorandum: FDA does not have adequate information to make a full evaluation of therapeutic equivalence. FDA's invitation to Mallinckrodt to submit additional bioequivalence data is still pending. Consequently, Count V of the Complaint alleging that the agency did not follow its own Orange Book procedures in assigning Mallinckrodt's products a BX rating fails.

III. Mallinckrodt Has Failed to Demonstrate that It Is Likely to Suffer Irreparable Harm in the Absence of Preliminary Relief

Plaintiff alleges impending financial losses in an effort to justify its extraordinary proposed relief, but mere economic loss ordinarily does not constitute irreparable harm. *See, e.g., Wis. Gas Co. v. F.E.R.C,* 758 F.2d 669, 674 (D.C. Cir. 1985); *Astellas v. FDA*, 642 F. Supp. 2d 10, 22 (D.D.C. 2009) ("[I]t is well-settled that economic loss alone will rarely constitute irreparable harm"); *Mylan Pharms. v. Thompson,* 207 F.Supp.2d 476, 485 (N.D. W. Va. 2001) ("purely economic injury and economic loss alone, however substantial, does not constitute irreparable harm."). Similarly, "courts have been hesitant to award injunctive relief based on assertions of lost opportunities and market share." *Id.*

Instead, economic loss may constitute irreparable harm "only where the loss threatens the very existence of the movant's business." *TFFI Corp. v. Williams,* Civil No. 8:13-cv-01809-AW, 2013 WL 6145548, at *4 (D. Md. Nov. 20, 2013) (*citing Wis. Gas Co.*, 758 F.2d at 674); *Coal. for Common Sense in Gov't Procurement v. United States*, 576 F. Supp. 2d 162, 168- 69 (D.D.C. 2008) ("degree of harm" must be so severe as to cause extreme hardship to the business or

threaten the very existence of Coalition members); *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 32 (D.D.C. 2006) (noting that "[t]o successfully shoehorn potential economic loss into the irreparable harm requirement, a plaintiff must establish that the economic harm is so severe as to 'cause extreme hardship to the business' or threaten its very existence." (citations omitted)); *Sociedad Anonima Viña Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business"); *Mylan v. Leavitt*, 484 F. Supp.2d 109, 123 (D.D.C. 2007)) ("[m]onetary figures are relative, and depend for their ultimate quantum, on a comparison with the overall financial wherewithal of the corporation involved.").

Plaintiff fails to show that its potential losses are significant in the context of its business. Plaintiff is a large multinational company with 5,500 employees worldwide and operations in 65 countries. Ex. B, Mallinckrodt PLC, *Mallinckrodt plc Reports Fiscal 2014 Fourth Quarter and Fiscal 2014 Financial Results* (Nov. 19, 2014), http://phx.corporate-ir.net/phoenix.zhtml?c=251847&p=irol-newsArticle_print&ID=1991004 [hereinafter "2014 Financial Results"] at 3). For the fiscal year ending September 26, 2014, the company had nearly $13 billion in total assets, and $2.5 billion in net sales. (*Id.* at 12 and 10).

Plaintiff has two major product lines: specialty pharmaceuticals and global medical imaging. Annual Report at 47. According to the company's Securities and Exchange filings, the specialty pharmaceuticals group "produces and markets branded and generic pharmaceuticals and API" (active pharmaceutical ingredients). Annual Report at 47. Methylphenidate ER is one of many profitable pharmaceutical products that the company sells, including API products and

branded products. Annual Report at 54. For the fiscal year ending in September 26, 2014, net sales of methylphenidate ER represented approximately $209.6 million out of $1.6 billion in total net sales for the company's specialty pharmaceuticals product line, or roughly 13%. (*Id.* at 10-11). When the company's global medical imaging net sales are included, methylphenidate ER's fiscal year 2014 net sales represented merely 8% of the company's total net sales.

Furthermore, Plaintiff's public statements regarding the impact of FDA's recent action further undermine their attempts to assert irreparable harm here. In a November 19, 2014 conference call regarding Plaintiff's 2014 Fourth Quarter earnings, Plaintiff's President and CEO and Plaintiff's Senior Vice President and CFO repeatedly minimized the impact of FDA's recent reclassification decision on methylphenidate ER. Ex. C, TheStreet, Inc., *Mallinckrodt (MNK) Earnings Report: Q4 2014 Conference Call Transcript* (Nov. 19, 2014), http://www.thestreet.com/print/story/12960259.html. On that call, Plaintiff's President and CEO Mark Trudeau noted "a number of opportunities to mitigate" the impact of the reclassification. *Id.* at 2. Trudeau explained that Mallinckrodt has a "very broad and diversified portfolio now and while the methylphenidate ER news was certainly a downside for us, we've got a number of other potentially very promising things going on in the overall portfolio." *Id*. at 5. Similarly, on the same call, Plaintiff's Senior Vice President and CFO Matt Harbaugh explained that the impact of FDA's action was far from the catastrophic event depicted in Plaintiff's brief, stating that "we can mute it more so now than we ever could before this time last year." *Id*. at 6. Thus, the alleged harm suggested by plaintiff's brief is belied by Plaintiff's broad, diverse, and robust financial picture and by the statements of its leaders.

Whatever the potential loss to a single product line as a result of the change in Orange Book code, it would not cause "extreme hardship" to Plaintiff overall, much less threaten its existence. *See, e.g., Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 32 (D.D.C. 2006) (for subsidiary of large pharmaceutical company, $31 million loss representing less than one percent of its sales was "not irreparable harm . . . nor would it threaten the company's very existence") (internal quotations and citation omitted); *cf. Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (recognizing injury to a company with a single product line). When, as here, a company seeking emergency injunctive relief does not establish that its alleged losses "would threaten the continued existence of [its] business," it "fail[s] to demonstrate irreparable injury." *Mylan*, 484 F. Supp. 2d at 123 .

Moreover, Plaintiff must establish that it would suffer irreparable harm during the pendency of the litigation – *i.e.*, before its claims can be heard on the merits. *Mylan v. Shalala*, 81 F. Supp. 2d 30, 43 (D.D.C. 2000); *see also Apotex, Inc. v. FDA*, No. 06-0627, 2006 WL 1030151 at *17 (D.D.C. Apr. 19, 2006) ("the actual relevant period for assessing harms is probably only a few months" – from the precipitating event to the time the case is resolved on the merits); *Bristol- Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 221 (D.D.C. 1996)("If it ultimately prevails on the merits, Bristol's total sales will be insignificantly affected over the duration of the litigation."). Thus, whatever revenue reduction Plaintiff might *eventually* suffer due to the Orange Book recoding is immaterial. In order to justify the extraordinary remedy of a temporary restraining order, Plaintiff must demonstrate that, in the absence of such relief, it would suffer virtually catastrophic harm before its claims would otherwise be heard.

Plaintiff falls far short of substantiating "loss [that] threatens the very existence of [its] business" before the Court resolves this case on the merits. Instead, Plaintiff relies upon the conclusory assertion that generic entry will significantly impact Plaintiff's revenue stream and operations. *See Mike's Train House, Inc. v. Broadway Ltd. Imports, LLC*, 708 F. Supp. 2d 527, 532 (D. Md. 2010) ("Mere speculation about possible market share losses is insufficient evidence of irreparable harm."); *Bristol-Myers*, 923 F. Supp. at 221 (holding that a drug manufacturer failed to establish irreparable harm based on mere speculation that introduction of a generic drug would claim 50 to 70% of its market share). Plaintiff cannot claim that the loss of revenue from methylphenidate ER will "threaten[] the very existence" of the company because methylphenidate accounted for only approximately 8 percent of the company's revenue last year.

Nor is there any merit to Plaintiff's suggestion that economic losses are irreparable *per se* where sovereign immunity renders damages unrecoverable from a government defendant. *See* Pls.' TRO Br. at 38-39. If that were true, prospective injunctive relief would cease to be an extraordinary remedy in cases against the federal government. *See N. Air Cargo v. U.S. Postal Serv.*, 756 F. Supp. 2d 116, 125 n.6 (D.D.C. 2010), *vacated on other grounds*, 674 F.3d 852 (2012). Courts have concluded that even if the harm is irrecoverable because the government is immune from suits seeking monetary damages, "it remains incumbent on plaintiffs to demonstrate . . . that they are threatened with serious injury." *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 25 (D.D.C. 2012). Plaintiff's reliance on *Smoking Everywhere* is misplaced, as the *Smoking Everywhere* court's "irreparable injury determination was based in large part on the fact that the potential economic loss and loss of good will are substantial, especially for a fledgling company

like [plaintiff, founded just one year prior,] that has only one product line." *See ViroPharma*, at 26 n.31. Plaintiff is no such fledgling company. Furthermore, courts have recently criticized the characterization in *Feinerman v. Bernardi* 558 F. Supp. 2d 36, 51 (D.D.C. 2008), relied on by Plaintiff, of economic damages that are unrecoverable due to sovereign immunity being "irreparable *per se*" and have instead suggested that "the inability to recover economic losses can more accurately be considered as a factor in determining whether the movant has shown irreparable harm." *ConverDyn v. Moniz*, --- F.Supp.3d ----, 2014 WL 4477555 at *11 (D.D.C. Sept. 12, 2014). Because Plaintiff's "broad and diverse" portfolio allows Plaintiff to "mute" whatever economic impact FDA's reclassification might have, Plaintiff fails to meet its burden to show that its very existence is threatened and, therefore, fails to establish irreparable harm.

IV. The Balance of Harms and Public Interest Weighs Heavily Against the Extraordinary Relief Requested

The public benefits most from the proper resolution of scientific issues and having the agency make correct, well-supported decisions regarding whether drugs are TE to for one another. *See Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998) (vacating preliminary injunction after determining, *inter alia*, that public interest was not furthered by injunction and that court was not in a position to question the FDA's scientific assessments). The public interest is simply not advanced by forcing FDA to maintain an AB TE rating for Mallinckrodt's product in the face of unresolved scientific TE questions. The public has an interest in receiving accurate public health information so patients can make better- informed treatment decisions in consultation with their health care practitioners, an interest that far outweighs a private company's financial interests.

The balance of hardships and the public interest both tilt decisively against entry of the requested injunctive relief.

CONCLUSION

For the foregoing reasons, Plaintiff's motion should be denied.

Dated: November 20, 2014

Respectfully submitted,

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